IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIAL-PORTELA & CA. S.A., BIAL-HOLDING, S.A. and SUNOVION PHARMACEUTICALS INC., Plaintiffs,	)	
v.	)	Civ. No. 18-304-CFC-CJB
ALKEM LABORATORIES LIMITED, Defendant.	)	

BIAL-PORTELA & CA. S.A., BIAL-HOLDING, S.A. and SUNOVION PHARMACEUTICALS INC., Plaintiffs,	)	
v.	)	Civ. No. 20-786-CFC-CJB
ALKEM LABORATORIES LIMITED, Defendant.	)	

BIAL-PORTELA & CA. S.A., BIAL-HOLDING, S.A. and SUNOVION PHARMACEUTICALS INC.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 21-186-CFC
ALKEM LABORATORIES LIMITED,	)	
Defendant.	)	

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OPINION

September 15, 2022
Wilmington, Delaware

COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of the submission by Defendant Alkem Laboratories Limited (Alkem) of an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration (FDA) for approval to market a generic version of APTIOM®, a pharmaceutical that is orally administered once a day in tablet form to treat epileptic seizures called partial-onset seizures. APTIOM® is marketed by Plaintiffs BIAL - PORTELA & CA S.A., BIAL - HOLDING, S.A., and Sunovion Pharmaceuticals Inc. (collectively, Bial). The active pharmaceutical ingredient (API) in APTIOM® is eslicarbazepine acetate.

Bial has asserted six claims across five patents. It alleges that Alkem's submission of its ANDA to the FDA constitutes infringement under 35 U.S.C. § 271(e)(2)(A) of claim 3 of U.S. Patent No. 10,675,287 (the #287 patent), claim 5 of U.S. Patent No. 10,695,354 (the #354 patent), claims 7 and 8 of U.S. Patent No. 10,702,536 (the #536 patent), claim 20 of U.S. Patent No. 9,763,954 (the #954 patent), and claim 17 of U.S. Patent No. 10,912,781 (the #781 patent). None of the six asserted claims cover the compound eslicarbazepine acetate; rather, five of the claims cover methods of administering eslicarbazepine acetate and one of the claims is a formulation claim for a tablet with eslicarbazepine acetate as the API. Alkem denies that it infringes claim 17 of the #781 patent and claim 20 of the #954

patent and further alleges that all six asserted claims are invalid. It has also filed counterclaims seeking declaratory judgments of noninfringement and invalidity of the asserted patents.

I held a three-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law. I write primarily for the parties.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arise were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., and specifically by the so–called Hatch–Waxman Amendments to the FDCA. Justice Kagan provided in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the uses for which the drug may be marketed. The FDA may approve a brand–name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.

Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch–Waxman Amendments. Those amendments allow a generic competitor to file an abbreviated new drug application (ANDA) piggy–backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand–name drug. As we have previously recognized, this process is designed to speed the introduction of low–cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand–name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method–of–use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch–Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method–of–use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and

> expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).
>
> After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.
>
> * * * *[One of those ways] is to file a so–called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve–out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue [under 35 U.S.C. § 271(e)(2)(A)]. Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (irrelevant citations and internal quotation marks omitted).

II. FINDINGS OF FACT

A. Introduction

1) BIAL - PORTELA & CA S.A., is a Portuguese corporation, No. 18–304[1], D.I. 235, Ex. 1 ¶ 1, and the assignee of the asserted patents, D.I. 235, Ex. 1 ¶¶ 17, 26, 36, 47, 58.

2) BIAL - HOLDING, S.A. is a Portuguese corporation having its principal place of business in Portugal. D.I. 235, Ex. 1 ¶ 2. Although BIAL - HOLDING has been a named Plaintiff since the filing of the initial complaint, *see* D.I. 1, no evidence about BIAL - HOLDING or its connection to this lawsuit was adduced during trial. The only reference specific to BIAL - HOLDING in the pretrial order simply identifies it as a Portuguese corporation having its principal place of business in Portugal. D.I. 235, Ex. 1 ¶ 2. Nonetheless, the pretrial order defines "Plaintiffs" as BIAL - PORTELA, BIAL - HOLDING, and Sunovion and also states that "no party contests Plaintiffs' standing for purposes of these actions, and the parties agree that no proof of standing needs to be adduced at trial." D.I. 235 ¶ 26.

[1] Although the three cases have not been consolidated, they were tried together. Because identical briefs were filed in all three cases, I cite only to one docket. Thus, all D.I. citations refer to the No. 18-304 case docket.

3) Sunovion, a Delaware corporation with its principal place of business in Massachusetts, D.I. 235, Ex. 1 ¶ 3, is the holder of NDA No. 022416 for APTIOM® (eslicarbazepine acetate) Tablets in 200, 400, 600, and 800 mg dosage forms. The FDA approved this NDA for use as an adjunctive therapy for partial-onset seizures in November 2013 and for use as a monotherapy for partial-onset seizures and pediatric use in August 2015. D.I. 235, Ex. 1 ¶¶ 67–70.

4) The Orange Book for APTIOM® lists the #954, #287, #354, #536, and #781 patents. D.I. 235, Ex. 1 ¶ 71.

5) Sunovion is the exclusive licensee of the asserted patents in the United States. D.I. 235, Ex. 1 ¶ 67.

6) Alkem is an Indian corporation with its principal place of business in India. D.I. 235, Ex. 1 ¶ 4.

7) Alkem has submitted ANDA No. 211199, seeking approval to engage in the commercial manufacture, use, sale, and/or importation of eslicarbazepine acetate tablets in 200, 400, 600, and 800 mg dosage forms. D.I. 235, Ex. 1 ¶ 73. Alkem's ANDA No. 211199 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the #954, #287, #354, #536, and #781 patents are invalid, unenforceable, and/or would not be infringed. D.I. 235, Ex. 1 ¶ 74.

B. Witnesses

1. Fact Witnesses

8) Mark Duffy is the director of strategy and business development for Bial. Tr. at 50:20–23. Duffy testified about the licensing agreement for APTIOM® that Bial has with Sunovion. *See, e.g.*, Tr. at 50:24–51:4.

11) Patricio Soares da Silva is a named inventor on the #954, #287, #354, and #536 patents. JTX 6; JTX 7; JTX 8; JTX 9. Soares da Silva started working for Bial in 1993. Tr. at 83:2–6. While there, he helped develop the compound eslicarbazepine acetate and APTIOM®. Tr. at 84:9–18.

12) Ricardo Lima is a named inventor on the #781 patent. JTX 10. Lima began working for Bial in 2000. Tr. at 172:14–16. While there, he helped develop the compound eslicarbazepine acetate and APTIOM®. Tr. at 173:1–9.

13) Jose Luis da Almeida was a practicing physician for a few years before entering the pharmaceutical industry, where he worked with Soares da Silva. Tr. at 391:3–14. He is a named author on the Almeida 2002 abstract. Tr. at 391:15–24.

14) Ujwal Chhabra testified on Alkem's behalf about Alkem's ANDA label and the use of microcrystalline cellulose. Tr. at 400:8–11. Alkem adduced no evidence at trial about Chhabra's qualifications, his employment, or ties to Alkem, and thus I have no idea how he is connected to Alkem or this action. *See*

Tr. at 400:12–04:3; D.I. 235. I would have struck his testimony for lack of foundation had Bial objected to it.

15) Prashant Mandagade works with Alkem's laboratories in Mumbai. Tr. at 404:9–10. Mandagade worked as the head of the formulation development department and was involved in the formulation development for eslicarbazepine acetate. Tr. at 406:4–9.

16) Emily Bulat testified as Sunovion's 30(b)(6) witness on marketing and sales. Tr. at 715:17–22. Prior to leaving Sunovion, Bulat was the Executive Director of US neurology marketing. Tr. at 716:13–15.

2. Bial's Expert Witnesses

17) John Koleng has a Ph.D. in pharmaceutical drug delivery. Tr. at 286:1–6; PTX 388. Koleng has worked in pharmaceutical development since 1996, working on drug product formulation, manufacturing, and testing dosage forms. Tr. at 286:7–11; PTX 388. Koleng is an expert in the design, evaluation, and formulation of drug products. Tr. at 289:19–24.

18) James Wheless is a licensed physician who specializes in neurology with a subspecialty of epilepsy. Tr. at 214:3–5; PTX 426. Wheless sees over 100 patients in his clinic a month, and almost all are epilepsy patients. Tr. at 216:12–18. Wheless has been involved in clinical drug development for over 30 years and has been involved in over 150 clinical trials—most of which were related to

partial-onset epilepsy and intractable epilepsy. Tr. at 216:22–17:7; PTX 426. Wheless is an expert in clinical and research-based neurology, including the treatment of patients suffering from epilepsy with partial-onset seizures and patients with intractable epilepsy. Tr. at 218:16–21.

19) John Jarosz is an economist with graduate degrees in law and economics. Tr. at 361:1–8; PTX 1161. Jarosz is an expert in the economics of intellectual property protection and valuation. Tr. at 62:4–8.

20) Robert Williams has a Ph.D. in pharmaceuticals, is a professor of pharmaceutics, and serves as division head of molecular pharmaceutics and drug delivery at the University of Texas at Austin. Tr. at 816:24–18:16; PTX 550. Williams is an expert in the design, evaluation, and formulation of drug products. Tr. at 818:25–19:5.

21) Barry Gidal has a Doctor of Pharmacy degree and completed a post-doctoral fellowship in clinical pharmacokinetics in epilepsy. Tr. at 806:16–07:6; PTX 1160. Gidal is an expert in clinical pharmacokinetics of anti-epileptic medications. Tr. at 809:22–25.

3. Alkem's Expert Witnesses

22) Ivan Hofmann is an economist with a focus on pharmaceutical economics and intellectual property economics. Tr. at 720:11–22, 721:5–8; DTX 240.

23) Jason McConville has a Ph.D. in pharmaceutics that covers drug delivery systems and aspects of pharmacokinetics. Tr. at 639:8–11; DTX 101. McConville is a professor of pharmaceutics at the University of New Mexico and has a research lab there in which he studies drug formulation and drug delivery. Tr. at 639:22–25. McConville is an expert in pharmaceutical compositions and methods of making them. Tr. at 642:24–43:4.

24) Michael Rogawski has a Ph.D. in pharmacology and a medical degree from Yale. Tr. at 559:8–11; DTX 2. Rogawski was previously employed as the chief of epilepsy research at the National Institutes of Health and is currently a professor in the UC Davis Department of Neurology. Tr. at 559:12–24. Rogawski is an expert in neurology and pharmacology, specializing in anti-seizure medications. Tr. at 570:12–16.

25) Patrick Ronaldson has a Ph.D. in pharmaceutical sciences and is a professor of pharmacology at the University of Arizona, teaching in the medical school and pharmacology graduate program. Tr. at 409:1–9, 411:15–19; DTX 204A. Ronaldson has been a researcher in the field of neuropharmacology for 20 years. Tr. at 420:21–25. Over Bial's objection, Alkem offered Ronaldson as an expert in the field of neuropharmacology, which includes the pharmacology of anticonvulsive drugs. Tr. at 426:25–27:10.

C. The Asserted Patents

1. The #287, #354, and #536 Patents (The Once-Daily Methods of Dosing Patents)

26) The parties and witnesses refer to these three patents together as the "once-daily patents."

27) The once-daily patents are directed to administering eslicarbazepine acetate once-daily to treat partial-onset seizures. JTX 7; JTX 8; JTX 9.

28) Bial asserts infringement of claim 3 of the #287 patent. D.I. 235, Ex. 1 ¶ 30. Unasserted independent claim 1 of the #287 patent reads:

> A method for treating a patient with partial-onset seizures comprising administering once-daily about 1,200 mg of eslicarbazepine acetate to the patient, wherein the patient is a human.

D.I. 235, Ex. 1 ¶ 31. Claim 3 depends from claim 1 and reads: "The method of claim 1, wherein the about 1,200 mg of eslicarbazepine acetate is administered orally." D.I. 235, Ex. 1 ¶ 32. Alkem does not contest infringement of this claim. D.I. 235, Ex. 1 ¶¶ 33–34.

29) Bial asserts infringement of claim 5 of the #354 patent. D.I. 235, Ex. 1 ¶ 41. Unasserted independent claim 1 of the #354 patent reads:

> A method for treating a patient with partial-onset seizures, comprising administering once-daily from about 800 mg to about 1800 mg of eslicarbazepine acetate to the patient, wherein the patient is a human.

D.I. 235, Ex. 1 ¶ 42. Claim 5 depends from claim 1 and reads: "The method of claim 1, comprising administering once-daily about 800 mg of eslicarbazepine acetate to the patient." D.I. 235, Ex. 1 ¶ 43. Alkem does not contest infringement of this claim. D.I. 235, Ex. 1 ¶¶ 44–45.

30) Bial asserts infringement of claims 7 and 8 of the #536 patent. D.I. 235, Ex. 1 ¶ 51. Unasserted independent claim 1 of the #536 patent reads:

> A method for treating a patient with partial-onset seizures, comprising: administering once-daily to a patient in need thereof a pharmaceutical composition consisting essentially of eslicarbazepine acetate, wherein the once-daily administration is pharmacologically effective to treat partial-onset seizures in the patient, and wherein the patient is a human.

D.I. 235, Ex. 1 ¶ 52. Claim 7 depends from claim 1 and reads: "The method of claim 1, wherein the pharmaceutical composition is administered once-daily in an amount consisting essentially of about 400 mg of eslicarbazepine acetate." D.I. 235, Ex. 1 ¶ 53. Claim 8 depends from claim 1 and reads: "The method of claim 1, wherein the pharmaceutical composition is administered once-daily in an amount consisting essentially of about 600 mg of eslicarbazepine acetate." D.I. 235, Ex. 1 ¶ 54. Alkem does not contest infringement of these claims. D.I. 239 ¶¶ 5–6.

31) The once-daily patents share the same written description. D.I. 235, Ex. 1 ¶ 29.

32) The priority date of the once-daily patents is May 6, 2005. JTX 7; JTX 8; JTX 9.

33) The parties stipulated that if Alkem proves one claim of the once-daily patents is invalid, all of the asserted claims of these patents are invalid. D.I. 241 at 3. Alkem selected claim 3 of the #287 patent as the representative claim. Tr. at 461:2–5 (Ronaldson).

2. The #954 Patent (The Method of Treatment Patent)

34) The #954 patent is directed to using eslicarbazepine acetate to treat a patient who has previously been treated with oxcarbazepine but has ongoing seizures. Tr. at 234:3–6 (Wheless); JTX 6.

35) Bial asserts infringement of claim 20 of the #954 patent. D.I. 235, Ex. 1 ¶ 63. That claim reads:

> A method for treating an intractable epilepsy condition comprising administering to a subject in need thereof a therapeutically effective amount of eslicarbazepine or eslicarbazepine acetate wherein the subject has previously been treated with oxcarbazepine, and wherein the eslicarbazepine or eslicarbazepine acetate is administered as a monotherapy for treating said condition.

D.I. 235, Ex. 1 ¶ 64.

36) The parties agree that: (1) the phrase "wherein the subject has previously been treated with oxcarbazepine" means "wherein the subject is intractable to oxcarbazepine," D.I. 239 ¶ 9, (2) the term "intractable" means

"difficult–to–treat or treatment(drug)–resistant and thus encompasses both pharmacoresistant and refractory conditions," D.I. 55 at 4, (3) the term "pharmacoresistant" means "a condition where the patient is not responsive to pharmaceutical treatment at all," D.I. 55 at 4, and (4) the term "refractory" means "a condition where the patient becomes progressively less responsive to their medication and, in the case of epilepsy, suffers from an increasing number of seizures," D.I. 55 at 4.

3. The #781 Patent (The Formulation Patent)

37) Bial asserts infringement of claim 17 of the #781 patent. D.I. 235, Ex. 1 ¶ 20. Unasserted independent claim 1 of the #781 patent reads:

> A pharmaceutical composition consisting essentially of eslicarbazepine acetate in combination with a binder and a disintegrant, wherein eslicarbazepine acetate is present in an amount of from 80 to 90 wt%, the binder is present in an amount of from 3 to 10 wt%, and the disintegrant is present in an amount of from 3 to 10 wt%, and wherein the pharmaceutical composition exhibits a dissolution of at least about 60% at about 30 minutes at a temperature of 37±0.5° C and a pH of about 4.5 using a paddle apparatus at a speed of about 100 rpm.

D.I. 235, Ex. 1 ¶ 21. Claim 17 depends from claim 1 and reads: "The pharmaceutical composition of claim 1, further comprising a lubricant, and/or glidant." D.I. 235, Ex. 1 ¶ 22.

D. Artisans of Ordinary Skill[2]

1. The #287, #354, and #536 Patents (the Once-Daily Patents)

38) During trial, I made a factual finding that an artisan of ordinary skill for these patents would have a medical degree in the field of neurology with at least two years of experience treating patients with epilepsy and have a Ph.D. in pharmaceutical sciences, chemistry, or a related field, with at least two years of post-graduate laboratory/industrial experience. Tr. at 882:17–21.

39) I confirm my finding that the artisan of ordinary skill would have a medical degree. First, both inventors had medical degrees. Tr. at 874:2–4. Second, the shared written description of the three patents discusses clinical studies, JTX 9 at 2:29–37, 7:37–10:4, and a medical doctor would be needed to "engage in clinical studies," Tr. at 872:8–14; *see also* Tr. at 872:21–73:23 (Alkem's counsel agreeing that a medical doctor would be needed to "participate in the clinical trial[,]" that "Ronaldson cannot, himself, supervise a Phase I study[,]" and that "legally supervis[ing] a Phase I study" is different than "review[ing] Phase I study results and interpret[ing] them[.]"). Third, the written description teaches that the compound will be administered by "any route known to those skilled in the art." JTX 9 at 6:40–45; *see also* Tr. at 880:7–9 ("There's

[2] Determination of the level of ordinary skill in the pertinent art is a factual inquiry. *Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

also clinical discussions that would say we need a doctor administering the compound by methods known to an artisan of ordinary skill[.]"). Fourth, the written description refers to "a pharmacologically effective amount" and teaches that the amount "will vary according to various well-known and understood factors, such as, for example, the condition being treated and the physiological characteristics of the patient" but that the amount "will be well within the ability of one skilled in the art to determine." JTX 9 at 7:3–12; *see also* Tr. at 880:10–13 ("The determination of the effective amount based on physiological characteristics of the patient being treated . . . would say you need a doctor.").

40) I also confirm my finding at trial that the artisan of ordinary skill would have a Ph.D. in a pharmaceutical science or related field. One inventor had a Ph.D., and there is extensive pharmacological discussion throughout the patents' shared written description. *See* JTX 9 at 3:1–5 (discussion of half-lives); 3:40–45 (discussion of the rate of exposure, the C_{max}, the extent of exposure, and the area under the curve (AUC)), 5:30–6:30 (same); 4:37–5:4 (discussion of formulation of pharmaceutical compositions); 11:10–15:19 (derivation of pharmacokinetic parameters); 1:23–27 (discussion of metabolite toxicity and drug potency); 2:53–62 (discussion of sustained relief delivery systems of predecessor drugs).

41) Alkem's expert, Ronaldson, has a Ph.D. in pharmaceutical sciences. Tr. at 411:15–19 (Ronaldson). But Ronaldson does not have a medical degree, is

not a practicing physician, and has never treated a patient with epilepsy or prescribed an antiepileptic drug to a patient. Tr. at 536:8–18 (Ronaldson). Ronaldson did not rely on any other expert, including any medical doctor or Alkem's expert Rogawski, in developing his opinions, and he limited his opinions "to the pharmacology of eslicarbazepine acetate and to the knowledge, experience, and skills of a person of ordinary skill in the art with a Ph.D. in pharmacology." 538:11–18 (Ronaldson). Accordingly, Ronaldson does not meet the definition of an artisan of ordinary skill.

42) Bial's expert, Wheless, is a licensed physician who specializes in neurology with a subspecialty in epilepsy. Tr. at 214:3–5. Wheless does not have a Ph.D. in pharmaceutical sciences or a related field. *See* PTX 426. Lacking this qualification, Wheless, alone, does not meet the definition of an artisan of ordinary skill. Wheless's testimony that he considered and agreed with the opinions of Gidal does not save him because that testimony was cursory and conclusory. *See* Tr. at 776:19–77:2 (Wheless). Moreover, Wheless explicitly stated that he was giving his opinion from the perspective of a medical doctor in the field of

neurology with at least two years of experience treating patients with epilepsy. Tr. at 805:8–19.[3]

43) "To offer expert testimony from the perspective of a skilled artisan in a patent case—like for claim construction, validity, or infringement—a witness must at least have ordinary skill in the art." *Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022). Accordingly, I will exclude Wheless's and Ronaldson's testimony on both ultimate conclusions of validity of the once-daily dosing patents and "underlying technical questions" "such as the nature of the claimed invention, the scope and content of the prior art, the differences between the claimed invention and the prior art, or the motivation of one of ordinary skill in the art to combine . . . references to achieve the claimed invention." *HVLPO2, LLC v. Oxygen Frog, LLC*, 949 F.3d 685, 689 (Fed. Cir. 2020) (internal quotation marks and citation omitted). As a practical matter, this evidentiary ruling did not affect the ultimate disposition of Alkem's invalidity claims, and for completeness I make certain findings of fact below based on Wheless's and Ronaldson's testimony.

[3] I also note that Gidal testified that he did not do any analysis on what level of skill an ordinary artisan would have had and that he instead "applied" "Wheless's offered level of skill" in forming his opinions. Tr. 815:5–12.

2. The #954 Patent (the Method of Treatment Patent)

44) Wheless defined the artisan of ordinary skill for this patent as "a clinician that was prescribing medication . . . with a neurology background [and] at least a couple of years' experience in treating epilepsy, typically a physician" or "a medical doctor in the field of neurology with at least two years of experience treating patients with epilepsy." Tr. at 781:18–23, 805:8–15.

45) Alkem offers a definition for the artisan of ordinary skill for this patent in its proposed findings of fact without a record citation. *See* D.I. 264 ¶ 124. Accordingly, I will adopt Bial's definition.

46) Alkem's expert, Rogawski, is a medical doctor with a Ph.D. in pharmacology and experience in treating patients with epilepsy. Tr. at 559:8–11, 559:12–24.

47) Bial's expert, Wheless, is a medical doctor who treats epilepsy patients and is also a professor of pediatric neurology at the University of Tennessee. Tr. at 214:3–16:18.

48) Both experts qualify as artisans of ordinary skill under Bial's definition above.

3. The #781 Patent (The Formulation Patent)

49) The parties offered at trial similar definitions of the artisan of ordinary skill for this patent. Bial's expert testified that his opinion would not change if I

were to adopt Alkem's definition of a skilled artisan. *See* Tr. at 820:25–21:7 (Williams). Accordingly, I will adopt Alkem's definition of an artisan of ordinary skill as someone with a Ph.D. in pharmaceutical sciences or a closely related field and experience in research related to pharmaceutical dosage forms or someone with at least a Bachelor's or Master's degree in pharmaceutical sciences and three to five years of practical experience in formulating drugs. Tr. at 641:20–42:6 (McConville).

50) Bial's expert, Koleng, has a Ph.D. in pharmaceutical drug delivery and has worked in pharmaceutical development since 1996. Tr. at 286:1–11. Koleng qualifies as an artisan of ordinary skill for this patent.

51) Alkem's expert, McConville, has a Ph.D. in pharmaceutics and has a research lab in which he studies drug formulation and drug delivery. Tr. at 639:8–25. McConville qualifies as an artisan of ordinary skill for this patent.

E. Facts Relevant to Infringement

1. The #954 Patent (Method of Treatment)

52) Alkem's proposed label is copied from the APTIOM® label and does not contain any carve–outs for patients who are intractable to oxcarbazepine—i.e., the patient population covered by claim 20 of the #954 patent.

53) Physicians and healthcare providers will prescribe, and patients will use, Alkem's product per the FDA-approved labeling. Tr. at 401:22–25, 403:12–15 (Chhabra).

54) Bial's expert, Wheless, testified, and Alkem does not dispute, that doctors prescribe Aptiom® to patients who are intractable to oxcarbazepine—i.e., the patient population covered by claim 20 of the #954 patent. I find therefore that it is more likely than not that doctors would prescribe Alkem's generic product to patients who are intractable to oxcarbazepine.

55) Alkem's package insert has instructions regarding dosage strengths and dosing regimen to treat partial-onset seizures. PTX 173; Tr. at 403:8–11 (Chhabra).

56) Bial's expert, Wheless, testified that "there are several areas in [Alkem's] label" that "encourage" doctors to use Alkem's generic product to treat patients who are intractable to oxcarbazepine. Tr. at 238:6–7. I did not, however, find his testimony credible on this point.

57) Wheless testified specifically that Section 1 of Alkem's label would encourage the treatment of this patient population. That section is titled "Indications and Usage" and it states that "[s]slicarbazepine acetate tablets are indicated for the treatment of partial-onset seizures in patients 4 years of age and older." PTX 173 at 3. Section 1 does not provide any instructions or

recommendations for prescribing the product to patients that have previously been treated with oxcarbazepine. And, indeed, Wheless testified that "there's nothing there that would say I could *not* use it in folks that were previously on oxcarbazepine, or even currently on, and convert them to this product. So that would encourage me that that's something I could do." Tr. at 238:12–16 (emphasis added). I do not find it credible to testify under oath that the absence of an instruction *not* to prescribe a medication to a particular patient group constitutes an instruction or encouragement to prescribe the medication to that group.

58) Wheless next cited Section 4 of the label as an "area" that "would encourage" doctors to prescribe Alkem generic product to patients who are intractable to oxcarbazepine. That section includes a contraindication that instructs healthcare providers not to administer Alkem's generic product to a patient who has a hypersensitivity to oxcarbazepine or eslicarbazepine acetate. PTX 173 at 5. But that contraindication does not provide any instructions or recommendations for prescribing the product for the patient population at issue in the #954 patent. *See* Tr. at 602:13–17 (Rogawski testifying that a "contraindication in a group that is hypersensitive" to oxcarbazepine does not "recommend to a POSA, or a healthcare practitioner, [that] the product ought to be used in a population of patients who are intractable to oxcarbazepine").

59) Finally, Wheless testified, and Bial argues that the results of a study discussed in Section 14.1 of Alkem's label "will instruct healthcare providers to administer Alkem's generic APTIOM® product to th[e] population of patients" that is "intractable to oxcarbazepine because "6.6% of patients in the Section 14.1 study were . . . intractable to oxcarbazepine." D.I. 261 ¶¶ 144, 145. But it cannot be inferred from Section 14.1 that 6.6% of the patients in the study discussed in that section were intractable to oxcarbazepine, and thus Section 14.1 does not "instruct" healthcare providers to administer Alkem's generic product to that population of patients. As Alkem's expert, Rogawski, credibly testified:

> [S]ome of the patients [in the Section 14.1 study] were actually limited in terms of the dose that they were allowed on in the baseline period. And so some of these patients in the baseline period might have had a subtherapeutic dose of oxcarbazepine. So really, you can't use this study as a way of determining whether a patient who is refractory to oxcarbazepine would respond to eslicarbazepine [acetate] and have a better result.

Tr. at 604:19–05:1; *see also* PTX 173 at 26 (stating that patients in Section 14.1 study "experienced at least 4 seizures during the baseline period . . . while receiving 1 or 2 AEDs (both could not be sodium-channel blocking drugs, and at least one AED was limited to 2/3 of a typical dose).").

60) In sum, nothing in Alkem's label teaches, recommends, or encourages using its generic product in patients who are intractable to oxcarbazepine, and nothing in the label suggests that using the product in that patient population

specifically would be a "medically desirable activity." *See* Tr. at 605:24–06:5 (Rogawski). Accordingly, Alkem's label does not establish that Alkem intends for its product to be used in this patient population.

61) Bial adduced no other evidence at trial probative of whether *Alkem* intends for its product to be prescribed to the specific patient population claimed in claim 20 of the #954 patent. Thus, Bial did not establish by a preponderance of the evidence that Alkem intends to induce doctors to prescribe its generic product specifically to patients who are intractable to oxcarbazepine.

2. The #781 Patent (Formulation)

62) Alkem's proposed label states:

Table 2.3.P.1-1: Unit Composition of Eslicarbazepine Acetate Tablets 200 mg, 400 mg, 600 mg & 800 mg.

Name of the Ingredient	Specification	200 mg		400 mg		600 mg		800 mg		Function
		mg/tablet	% w/w	mg/tablet	% w/w	mg/tablet	% w/w	mg/tablet	% w/w	
A. Intra Granular Material:										
Eslicarbazepine Acetate*	IH	200.00	83.33 %	400.00	83.33 %	600.00	83.33 %	800.00	83.33 %	Active Pharmaceutical Ingredient
Croscarmellose Sodium	USP-NF	15.00	6.25 %	30.00	6.25 %	45.00	6.25 %	60.00	6.25 %	Disintegrant
Copovidone (Plasdone S630)	USP/NF	7.50	3.12 %	15.00	3.12 %	22.50	3.12 %	30.00	3.12 %	Binder
B. Binder Material:										
Copovidone (Plasdone S630)	USP/NF	8.75	3.64 %	17.50	3.64 %	26.25	3.64 %	35.00	3.64 %	Binder
Purified Water#	USP	q.s	q.s	qs	q.s	qs	q.s	qs	q.s	Solvent
C. Extragranular Material:										
Microcrystalline Cellulose** (Ceolus KG 802)	USP/NF	5.25	2.18 %	10.50	2.18 %	15.75	2.18 %	21.00	2.18 %	Diluent
Colloidal Silicon Dioxide	USP/ NF	1.10	0.45 %	2.22	0.45 %	3.30	0.45 %	4.40	0.45 %	Glidant
Sodium Stearyl Fumarate	USP/ NF	2.40	1.00 %	4.80	1.00 %	7.20	1.00 %	9.60	1.00 %	Lubricant
Total Weight of Tablet (Core)		240.00 mg	100%	480.00 mg	100%	720.00 mg	100%	960.00 mg	100%	

PTX 118 at 6.

63) As seen in the label, Alkem's generic tablets contain 2.18 wt % microcrystalline cellulose, which the label identifies as a diluent (i.e., a diluting agent). PTX 118 at 6.

64) It is undisputed that microcrystalline cellulose can act as both a diluent and a disintegrant. D.I. 265 at 19. The parties dispute, however, whether Bial proved at trial that microcrystalline cellulose acts a disintegrant in Alkem's ANDA product. Based on Koleng's testimony, I find that Bial established by a preponderance of the evidence that microcrystalline cellulose acts a disintegrant in Alkem's ANDA product.

65) Koleng credibly testified that pharmaceutical formulators use microcrystalline cellulose as a disintegrant because of its "good wicking properties and hydrogen bonds between adjacent matchstick–like bundles that break when exposed to water." PTX 896 at 2; *see also* PTX 1214 at 101, 175; Tr. at 331:9–15 (Koleng). He also credibly testified that microcrystalline cellulose's disintegrant properties are inherent and that therefore microcrystalline cellulose will "exhibit its wicking properties" and act as a disintegrant in a compound regardless of the amount of the microcrystalline cellulose in the compound. *See* Tr. at 331:9–15. As Koleng noted, even if the amount of microcrystalline cellulose is relatively small in a compound, its disintegrant functionality "remains." Tr. at 340:8–12.

66) Alkem did not offer at trial any testimony to rebut Koleng's testimony about microcrystalline cellulose's disintegrant properties, and thus no witness testified that microcrystalline cellulose would not or could not function as a disintegrant in Alkem's ANDA product.

67) Consistent with Koleng's testimony, the #781 patent's written description identifies microcrystalline cellulose as a "suitable disintegrant." JTX 10 at 6:9–41.

68) Multiple references identify microcrystalline cellulose as a disintegrant and support Koleng's testimony that microcrystalline cellulose's disintegrant functionality is an inherent property. *See* PTX 896 at 2 (research article titled "Functionality of Disintegrants and Their Mixtures in Enabling Fast Disintegration of Tablets by a Quality by Design Approach" teaching that "[m]icrocrystalline cellulose, commonly used as a filler in tablet formulations, is not considered to be a superdisintegrant but reported to possess good wicking properties and hydrogen bonds between adjacent matchstick–like bundles that break when exposed to water"); PTX 899 at 21 (book titled "Modern Pharmaceutics" teaching that "[s]ome forms of [microcrystalline cellulose] have been shown to be highly porous, with strong 'wicking' tendencies, thereby making them good disintegrants"); PTX 406 at 3 (book titled "Handbook of Pharmaceutical Excipients" teaching that, [i]n addition to its use as a

binder/diluent, microcrystalline cellulose also has some . . . disintegrant properties that make it useful in tableting"); *see also* Tr. at 330:5–19 (Koleng identifying the references).

69) Different publications recommend various concentration ranges for microcrystalline cellulose when it is used as a disintegrant. *See* PTX 898 at 13 (up to 10%); PTX 1214 at 115 (reporting "very good disintegrant properties" at concentrations "as low as 10%"); PTX 406 at 3 (5 to 15%). But Alkem did not identify any publication that stated or suggested that microcrystalline cellulose would not or could not function as a disintegrant if its concentration range were below the ranges identified in the publications.

F. Facts Relevant to Invalidity

1. The #287, #354, and #536 Patents (the Once-Daily Patents)

a. Prior Art

1) The #646 Patent

70) U.S. Patent No. 5,753,646 (the #646 patent) is prior art to the once-daily patents. DTX 427. The #646 patent described and claimed the active pharmaceutical ingredient eslicarbazepine acetate. DTX 427 at 1:35–64 (claiming "10–acetoxy10,11–dihydro–5H–dibenz/b,f/azepine–5–carboximide"); Tr. at 91:23–92:3 (Soares de Silva explaining that "10–acetoxy10,11–dihydro–5H–dibenz/b,f/azepine–5–carboximide" is eslicarbazepine acetate). The #646 patent

discloses that eslicarbazepine acetate has "valuable pharmaceutical properties" for the treatment of epilepsy. DTX 427 at 3:52–56.

71) The #646 patent discloses a method of treating a patient with epilepsy by administering a composition containing eslicarbazepine acetate. DTX 427 at claims 5 and 7. The #646 patent does not disclose once-daily dosing or a dosage amount. *See generally* DTX 427.

2) Almeida 2002

72) Almeida 2002, an abstract of a paper titled "P460 Pharmacokinetic profile of BIA 2-093, a putative new antiepileptic drug, after single and multiple administration in human healthy volunteers," is prior art to the once-daily patents. PTX 329; Tr. at 391:15–92:10 (presentation date).

73) Alkem contends that Almeida 2002 "expressly stated the reasonable expectation of success" for dosing eslicarbazepine acetate once-daily and that "[a]ll that remained [after Almeida 2002] was to confirm the efficacy of eslicarbazepine acetate through clinical trials." D.I. 263 at 13. *See also* D.I. 263 at 15 ("[T]he conclusion in Almeida 2002 that eslicarbazepine acetate was 'expected to be compatible with a once a day administration' confirms that a POSA would have had a reasonable expectation of success in dosing eslicarbazepine acetate once-daily.").

74) Almeida 2002 was presented at the Fifth European Congress on Epileptology in Spain in 2002 and is not a complete recitation of, but contains data from, two studies. Tr. at 391:15–92:76 (Almeida); Tr. at 110:10–13 (Soares da Silva); PTX 329. Those studies were intended to test the tolerability, safety, and pharmacokinetic properties of BIA 2-093 in healthy subjects. Tr. at 392:21–93:1 (Almeida); *see also* PTX 329 at 4 (study conducted in healthy volunteers). BIA 2-093 is eslicarbazepine acetate. Tr. at 170:3–8 (Soares da Silva).

75) Almeida 2002 teaches the oral administration of BIA 2-093 (eslicarbazepine acetate) up to 1,200 mg in human subjects. *See* PTX 329 at 4 (groups of eight healthy male subjects received single oral doses of up to 1,200 mg of BIA 2-093).

76) Almeida 2002 states that "[t]he pharmacokinetic profile described here for BIA 2-093 is expected to be compatible with once a day administration." PTX 329 at 5. The authors of Almeida 2002 testified that they expected that once-daily administration could be used safely, Tr. at 398:19–24 (Almeida), but that the data from Almeida 2002 was not "enough to show that you could treat partial-onset seizure patients once-daily" because the study had been conducted with healthy subjects. Tr. at 111:5–9 (Soares da Silva); Tr. at 398:2–18 (Almeida testifying "the results in healthy subjects cannot be extrapolated to patients" with epilepsy). I found the authors to be credible when testifying about this point and find that

Almeida 2002 discloses only that once-daily dosing is safe and tolerable, not that once-daily dosing is also efficacious to treat partial-onset seizures.

77) Alkem's expert, Ronaldson, admitted during his testimony that Almeida 2002 was a Phase I study conducted in healthy subjects to "look at safety and tolerability," "determine what dose range is going to be tolerable," and "get some additional pharmacokinetic information that you can use to guide further clinical trials on that drug." Tr. at 492:18–25.

78) Almeida 2002 does not disclose an expectation that once-daily administration of eslicarbazepine acetate would or could treat partial-onset seizures. *See* Tr. at 493:1–8 (Ronaldson testifying with regards to Almeida 2002: "[A] Phase I trial is essentially a gate. . . . [When] you are able to demonstrate that the drug doesn't cause any serious adverse events in healthy human subjects, and when you can establish a range of doses that's tolerated in those human subjects, that gives you the capability of being able to move forward with pertinent information in humans that would allow you to proceed to testing in a Phase II trial.")

3) Almeida 2003

79) Almeida 2003, titled "Safety, Tolerability and Pharmacokinetic Profile of BIA 2-093, a Novel Putative Antiepileptic Agent, during First

Administration to Humans," discloses a Phase I, single dose study in healthy volunteers, PTX 330, and is prior art to the once-daily patents. PTX 330.

80) Alkem contends that Almeida 2003 "provided additional pharmacokinetic data from the Phase I clinical studies, confirming that eslicarbazepine acetate was expected to be compatible with once-daily dosing." D.I. 263 at 22. *See also* D.I. 263 at 23 ("Ronaldson explained through an example that, based on the pharmacokinetic data presented in Almeida 2003, a once-daily dose of 1200 mg of eslicarbazepine acetate would have been preferred over a twice-daily dose of 600 mg of eslicarbazepine acetate . . . . [And] Almeida 2003 concluded that there were no adverse events within the tested dosage range of 20–1200 mg. For these reasons, Almeida 2003 is additional evidence of a motivation to dose eslicarbazepine acetate once-daily and a reasonable expectation of success.").

81) The Phase I study disclosed in Almeida 2003 examined the safety, tolerability, pharmacokinetics, and pharmacodynamics of treating healthy human volunteers with single doses of BIA 2-093. PTX 330 at 2; Tr. at 84:24–85:1 (definition of BIA 2-093). Almeida 2003 reported that "oral administration of BIA 2-093 at doses up to 1,200 mg appeared to be safe and was well tolerated by the subjects in this study." PTX 330 at 14. Almeida 2003 also presented data about the pharmacokinetics and the pharmacodynamics of eslicarbazepine acetate's

primary active metabolite, BIA 2–005, and minor metabolite, oxcarbazepine. PTX 330 at 7–12.

82) The field of the invention—pharmaceuticals used to treat epilepsy—is complex and requires a high skill level. *See* Tr. at 875:23–76:1 (Alkem counsel acknowledging that "pharmaceutical R&D is very arduous and takes a long time"), 876:5–16 (Bial counsel arguing that "the level of skill [for development of drugs] is high"), 881:3–9 (Bial counsel characterizing epilepsy as a "very complex disorder"). And, as noted above, an artisan of ordinary skill in the field would have both a medical degree and a Ph.D. in a pharmaceutical science. Lacking both of these qualifications, I am unable without expert testimony to determine with an abiding conviction that it is highly probable that Almeida 2003 discloses once-daily dosing to treat partial-onset seizures based on the reported pharmacological data. *See Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1330 (Fed. Cir. 2009) ("If the relevant technology were complex, the court might require expert opinions."); *cf.* Tr. at 825:13–15 (Williams declining to offer testimony about pharmacokinetics because, despite having a Ph.D. in pharmaceuticals generally, he is not a "pharmacokineticist").

83) I also find that even if I had not excluded Ronaldson's testimony, that testimony did not establish clearly and convincingly that Almeida 2003 discloses once-daily dosing to treat partial-onset seizures based on the reported

pharmacological data. Ronaldson affirmed without objection on direct examination in response to a blatantly leading question that "Almeida 2002 provided us this conclusion that eslicarbazepine acetate was expected to be compatible with once-daily dosing." Tr. 503:4–7. And he testified on direct examination that Almeida 2003 disclosed that the C_{max}[4] of a dose of 600 mg of eslicarbazepine acetate was lower than the C_{max} of a dose of 1,200 mg and that, even if two doses of 600 mg were administered twelve hours apart, the C_{max} of the two doses would be lower than the C_{max} of a single dose of 1,200 mg. Tr. at 504:1–05:11. But on cross-examination, Ronaldson conceded that he had not offered an opinion that "the concentrations that were detected in the Phase I trial [disclosed in Almeida 2003] would truly be efficacious." Tr. at 549:21–25.

4) Trileptal® Label

84) It is undisputed that the Trileptal® label is prior art to the once-daily patents. *See generally* D.I. 262. The active ingredient of Trileptal® is oxcarbazepine. DTX 438. Oxcarbazepine was known to be an effective treatment for partial-onset seizures. DTX 438 at 4. The Trileptal® label taught administering oxcarbazepine at least twice-daily. Tr. at 758:11–12 (Wheless); Tr. at 542:16–43:12 (Ronaldson); DTX 438 at 21.

[4] C_{max} is the maximum plasma concentration that is achieved after a dose. Tr. at 502:14–17 (Ronaldson).

85) Alkem contends that the Trileptal® label "is further evidence that eslicarbazepine acetate would have been expected to be effective for the treatment of partial-onset seizures" because eslicarbazepine acetate and oxcarbazepine metabolize into the same "primary active metabolite responsible for the antiepileptic activity[.]" D.I. 263 at 23. *See also* D.I. 263 at 24–25 ("[T]he half-life of [the active metabolite] was known to be longer when it was formed from eslicarbazepine acetate, and thus it would have been expected that eslicarbazepine acetate should be dosed differently than oxcarbazepine[,]" so "there would have been a motivation at least to confirm that once-daily dosing of eslicarbazepine acetate would be effective, based on the express disclosures in the prior art.").

86) But the Trileptal® label does not (1) reference eslicarbazepine acetate, (2) make any comparison between oxcarbazepine and eslicarbazepine acetate, or (3) suggest that eslicarbazepine acetate should be dosed differently than oxcarbazepine. *See* DTX 438. Accordingly, the Trileptal® label does not teach administering eslicarbazepine acetate once-daily. *See* Tr. at 549:4–8 (Ronaldson testifying: "I have not estimated any efficacy of eslicarbazepine acetate. All I stated is that because the two compounds [eslicarbazepine acetate and oxcarbazepine] produce the same active metabolite, there is a reasonable expectation of success that you would get efficacy from eslicarbazepine acetate.").

b. Obviousness of Asserted Claims

87) For the reasons stated in paragraphs 70 to 86, the #646 patent, Almeida 2002, Almeida 2003, and Trileptal®, considered individually or collectively, do not disclose that once-daily dosing of eslicarbazepine acetate is efficacious to treat partial-onset seizures. Alkem therefore did not show by clear and convincing evidence that an artisan of ordinary skill would have had a reasonable expectation of success in using once-daily dosing of eslicarbazepine acetate to treat partial-onset seizures.

88) The benefits of once-daily dosing generally include patient convenience and improved patient adherence to the medication regimen. Tr. at 224:1–5, 229:2–9 (Wheless). But Ronaldson admitted on cross-examination that fluctuations in blood plasma concentration of a compound where the concentration falls below the therapeutic range for the compound should be avoided when administering anti-epileptic drugs because a concentration below the therapeutic range would not be expected to be efficacious and would increase the risk of the patient experiencing breakthrough seizures. Tr. at 540:19–41:2, 545:3–10. He also admitted that "a greater fluctuation in blood plasma levels would occur with a higher C_{max} and lower C_{min}," Tr. at 541:3–8, and that "[a]s of the priority date of the once-daily patents . . . you would expect to see a greater fluctuation in blood levels with a once-daily dosing regimen as compared to a twice-daily dosing

regimen." Tr. at 541:3–22. Based on this testimony, I find that dosing once-daily has a higher risk of the blood plasma concentration of the active compound falling below the therapeutic level than dosing twice-daily has, and accordingly, I find that, even if an artisan of ordinary skill generally preferred to dose once-daily, the artisan would not have been motivated to dose an anti-epileptic drug (including eslicarbazepine acetate) once-daily.

89) On cross-examination, Ronaldson admitted, "In my testimony today, I didn't state anything regarding the fact that the concentrations that were detected in the Phase I trial would truly be efficacious. It's just that there's a reasonable expectation of success moving forward into a Phase II trial." Tr. at 549:17–25; *see also* Tr. at 513:3–9 (Ronaldson testifying "a person of ordinary skill in the art would have had a reasonable expectation of success of moving this drug forward towards . . . Phase II clinical trials"). I find that his testimony suggests only that an artisan of ordinary skill would have a reasonable expectation of success for *moving towards* a Phase II trial but not necessarily for *treating* partial-onset seizures. Further, an artisan of ordinary skill would be concerned about the risks associated with a blood plasma concentration falling below the therapeutic range. *See* Tr. at 540:19–41:2, 545:3–10, 541:3–8, 541:3–22 (Ronaldson).

90) I have no record evidence identifying a therapeutic range for eslicarbazepine acetate, so I cannot conclude that the pharmacokinetic information

reported in Almeida 2003 would inform an artisan of ordinary skill that administering 1,200 mg eslicarbazepine acetate once-daily would keep the blood concentration within the therapeutic range. Thus, there is no evidence that an artisan of ordinary skill would have a reasonable expectation of success *of treating* epilepsy with once-daily dosing of eslicarbazepine acetate as claimed in the patents. If anything, the record evidence suggests that an artisan of ordinary skill would doubt that dosing once-daily would be successful.

91) Thus, I find that Alkem did not show by clear and convincing evidence that an artisan of ordinary skill would have had the motivation to dose eslicarbazepine acetate once-daily with a reasonable expectation of success for treating partial-onset seizures.

c. Objective Indicia of Nonobviousness

1) Unexpected Results

92) One study cited in the once-daily patents was a Phase II study conducted by Soares da Silva. *See* Tr. at 113:4–15:8 (Soares da Silva). The study investigated the efficacy of dosing eslicarbazepine once-daily. PTX 489; Tr. at 113:15–25 (Soares da Silva). Soares da Silva testified that he was surprised to find that dosing once-daily had better results than dosing twice-daily for reducing seizures. Tr. at 114:22–15:2. Because Almeida 2002's conclusion does not

establish an expectation of efficacy from once-daily dosing, I will credit Soares da Silva's testimony that he was surprised by the Phase II results.

2) Industry Skepticism

93) Alkem does not dispute that APTIOM®'s recommended once-daily administration, as described in the product label, is covered by the asserted claims of the once-daily patents. *See generally* D.I. 264; *see also* Tr. at 234:19–22 (Wheless); PTX 453 at 7–8.

94) Wheless testified that physicians were skeptical of dosing APTIOM® once-daily. Tr. at 226:20–27:4. And Ronaldson testified that "[a]s of the priority date of the once-daily patents . . . you would expect to see a greater fluctuation in blood levels with a once daily dosing regimen as compared to a twice daily dosing regimen." Tr. at 541:3–22. Given the consistency of the experts' testimony, I will credit Wheless's testimony that physicians were skeptical of once-daily dosing.

3) Commercial Success

95) The record contains much testimony about the commercial success of APTIOM®. *See, e.g.*, PTX 1176 (showing that APTIOM® has one of the highest market shares of branded antiepileptic drugs); Tr. at 368:2–7 (Jarosz comparing APTIOM®'s success to its competitor's). Bial does not dispute that the #646 patent was a blocking patent, but Bial adduced record evidence suggesting that the once-daily dosing was a driver of the commercial success of APTIOM®. *See* Tr.

at 369:22–70:12 (Jarosz); PTX 594 at 33, 46, 59 (physicians identifying convenient dosing as a key reason they chose APTIOM® over other options). Thus, even if the #646 patent covers the compound, I find that the once-daily dosing method contributed to APTIOM®'s success.

96) APTIOM®'s revenue and profits rose over the past three years despite a drop in marketing spend. Tr. at 733:10–14 (Hofmann admitting that marketing spend has dropped); PTX 307 at 5–7. Thus, I conclude that, even if marketing spend played a role in APTIOM®'s commercial success, it is not solely responsible for APTIOM®'s success.

97) Because Bial has demonstrated that dosing eslicarbazepine acetate once-daily had surprising results, was received by skepticism, and contributed to APTIOM®'s commercial success, I find that the secondary considerations of nonobviousness suggest that an artisan of ordinary skill would not view the once-daily patents as obvious.

2. The #954 Patent (Method of Treatment)

98) The #954 patent reports that both oxcarbazepine and eslicarbazepine acetate are converted by metabolism to eslicarbazepine (i.e., S–licarbazepine). JTX 6 at 3:45–55, 1:45–47. Eslicarbazepine acetate is converted to S–licarbazepine and R–licarbazepine in a 19–to–1 ratio, and oxcarbazepine is converted to the same metabolites in a 4–to–1 ratio respectively. Tr. at 577:2–15

(Rogawski). S–licarbazepine and R–licarbazepine are enantiomers of one another (i.e., their structures are mirror images). Tr. at 588:9–89:6 (Rogawski).

99) The #954 patent implies that eslicarbazepine acetate will have improved effects over oxcarbazepine because, although both drugs metabolize into the same metabolites, eslicarbazepine acetate more favorably metabolizes into S–licarbazepine than oxcarbazepine does. JTX 6 at 4:8–37; Tr. at 88:16–89:2 (Soares da Silva). The #954 patent describes four examples that purport to demonstrate enhanced brain penetration or other enhanced effects for S–licarbazepine as compared to R–licarbazepine. The first example involved administering S–licarbazepine or R–licarbazepine to mice and measuring the blood/plasma ratio of these drugs over time. JTX 6 at 9:35–10:14. The second example involved administering to the mice P–glycoprotein and multidrug resistance protein inhibitors to determine whether such inhibitors affect the uptake of S–licarbazepine or R–licarbazepine into the brain.[5] JTX 6 at 9:47–63. The third example involved kindling studies in mice to which S–licarbazepine or R–licarbazepine had been administered. JTX 6 at 10:15–30. The fourth example involved injecting formalin into the paws of mice to induce paw licking. JTX 6 at 10:31–44.

[5] P–glycoprotein and multidrug resistance protein are drug transporters present in the brain, and the inhibitors competitively block the transport of other substrates by the transporters. JTX 6 at 2:5–7, 3:30–33.

100) The earliest priority date listed on the #954 patent is January 15, 2007. JTX 6.

a. Written Description

101) On cross-examination Soares da Silva acknowledged that "there [is] no study in humans described anywhere in the #954 patent where the human patient or subject of the study was intractable to oxcarbazepine and shown to respond to eslicarbazepine acetate[.]" Tr. at 153:16–21.

102) With regards to the experiments discussed in the patent, Soares da Silva testified that the only data in the #954 patent relevant to an intractable epilepsy condition are shown in Figures 4 and 5. Tr. at 145:4–16. The data shown in Figures 4 and 5 were obtained from a kindling mouse experiment modeling epileptogenesis.[6] Tr. at 146:10–13 (Soares da Silva). When asked, "[the kindling mouse model is] not actually a model of intractable epilepsy, is it?", Soares da Silva explained that, "[i]f the animal becomes resistant to the efficacy of the drug, then we can assume that the condition is intractable to that particular . . . drug," and he agreed that the kindling mouse model "is a model of intractable epilepsy if

[6] A kindling model involves "impulsing an electrical stimulus, either by an electrode implanted in the brain . . . or by applying a stimulus to the corneas of the eyes" repeatedly until the animal becomes epileptic. Tr. at 526:7–13 (Rogawski). Epileptogenesis is the process by which seizures become progressively more severe and eventually resistant to antiepileptic therapy. Tr. at 146:14–21 (Soares da Silva).

and when the animal becomes resistant to the drug[.]" Tr. at 147:1–18. When shown Figures 4 and 5, Soares da Silva identified day six as the day on which the mice became resistant to the drug. Tr. at 147:19–48:8. But Soares da Silva acknowledged that the data gathered after day six shows no difference in efficacy between S–licarbazepine and R–licarbazepine. Tr. at 149:6–18. Consistent with that admission, Rogawski explained that, based on Figures 4 and 5, once the mice are "fully kindled, they're now in a refractory state, and neither S–licarbazepine or R–licarbazepine, even at these very high doses, . . . [are showing] any activity . . . [so] the model is inconclusive." Tr. at 593:21–94:6. Accordingly, I find that the data after day six are not suggestive that S-licarbazepine treats intractable epilepsy better than R-licarbazepine treats it.

103) Further, although Soares da Silva explained that "S–licarbazepine treat[ment] . . . protect[ed against] the development of seizure severity in this model of intractability," Tr. at 140:24–41:5, Claim 20 does not teach *prevention of development* of intractable epilepsy but rather *treatment* of intractable epilepsy in patients not responsive to oxcarbazepine. Similarly, although Soares da Silva testified that the days before day six are "relevant because the patient has become intractable to some drugs," Tr. at 151:9–19, nothing in the patent suggests that, during those days, the mice were intractable to *oxcarbazepine* specifically. And any conclusion that could be drawn about mice could not be extended to humans.

See Tr. at 791:5–8 (Wheless) ("[I]f all we had was a kindling experiment, looking in a mouse model with kindling and giving the drug for a couple of weeks, I would say yes, that would not tell me how I leap from there to its use in humans."). Thus, even if I were to credit Soares da Silva's conclusion about the relative efficacy of S–licarbazepine and R–licarbazepine for the *prevention of development* of intractable epilepsy, Bial has not shown that such a conclusion is probative of relative efficacy of the metabolites for *treatment* of intractable epilepsy. Accordingly, I find that Figures 4 and 5 do not establish that eslicarbazepine acetate would treat patients intractable to oxcarbazepine.

104) Regarding the remaining studies described in the patent, even if Wheless were correct that those studies demonstrate a difference in brain penetration between S–licarbazepine and R–licarbazepine generally, *see* Tr. at 785:17–87:25, Soares da Silva admitted that the data that relates S–licarbazepine and R–licarbazepine to intractable epilepsy are represented only in Figures 4 and 5, *see* Tr. at 145:4–16. Thus, I conclude that the other studies are not probative of whether eslicarbazepine acetate treats patients intractable to oxcarbazepine.

105) Soares da Silva also offered testimony regarding a "P–gp hypothesis," explaining that "S–licarbazepine is not a substrate for P–gp" and so "patients with intractable epilepsy over expressing P–gp and treated with oxcarbazepine would

have less amount of the R–licarbazepine entity in their brains because of the over expression of P–gp." Tr. at 131:22–32:7. But the patent acknowledges that,

> [a]lthough the multidrug transporter [P–gp] hypothesis of intractable epilepsy is biologically plausible, it has not been proven. Despite the fact that high P–gp expression has been shown in epileptogenic brain tissue from patients with intractable epilepsy, adequate controls are lacking, as it is impossible to compare this tissue directly with tissue from patients who respond well to AED treatment (because these patients do not need to undergo surgical resection of epileptogenic foci). Consequently, *it is not clear whether the increased P–gp expression in patients with drug–resistant epilepsy is a cause of pharmacoresistance or just a result of uncontrolled seizures*—or an epiphenomenon that occurs in epileptic brain tissue irrespective of drug response.

JTX 6 at 3:11–24 (citation omitted; emphasis added); *see also* 2:42–46 ("Because multidrug transporters such as P–gp . . . accept a wide range of drugs as substrates, overexpression of such efflux transporters in the [blood brain barrier] *would be one likely explanation* for resistance to various AEDs in a patient with intractable epilepsy." (citation omitted; emphasis added)); 3:61–62 ("P-gp *may play* a role in the resistance to oxcarbazepine[.]" (emphasis added)). I find that this discussion in the patent is simply a research hypothesis. *See* Tr. at 578:14–59:1 (Rogawski) ("[The P-gp theory is] an interesting hypothesis, but as time has gone on, we've downgraded it in terms of its potential truth, because it hasn't really helped us with the understanding the issue of pharmaco-resistance.").

106) Thus, I find that Alkem has established by clear and convincing evidence that the data presented in the patent does not show that eslicarbazepine acetate could be used to effectively treat a patient intractable to oxcarbazepine and that the theories of why eslicarbazepine acetate might be effective in these patients are simply research hypotheses. *See* Tr. at 572:11–17 (Rogawski testifying, "[T]here [isn't] any information in the patent relevant to an intractable epilepsy condition in a patient who had been previously . . . treated with oxcarbazepine. In fact, oxcarbazepine wasn't really studied in the examples that were provided in the patent.").

b. Enablement

107) Although the written description teaches administering eslicarbazepine acetate once-daily and formulating "in any suitable manner, such as an oral dosage form, such as a tablet or capsule," JTX 6 at 12:66–13:4, 8:7–9, and, at the time of the invention, a Phase II study instructing how to dose this medication in epileptic patients existed, Tr. at 792:9–14 (Wheless), "the claim of the patent doesn't really explain how to practice the invention, [i.e.] how to treat a patient with an intractable epilepsy condition with [eslicarbazepine acetate] in a situation where they have failed to respond to oxcarbazepine," Tr. at 597:23–98:21 (Rogawski), and the patent lacks working examples, Tr. at 598:23–25 (Rogawski). Thus, I find that an artisan of ordinary skill's ability to dose eslicarbazepine acetate

for patients with epilepsy generally is not probative of an ability to dose for patients intractable to oxcarbazepine in the absence of any data suggesting that eslicarbazepine acetate would have any efficacy in this patient population. *Cf.* Tr. at 800:22–25 (Wheless admitting that the patent "does not describe any testing of eslicarbazepine acetate in human patients who were intractable to the oxcarbazepine").

108) Accordingly, for the same reasons discussed above regarding the patent's written description, I find that Alkem has shown by clear and convincing evidence that the patent does not teach an artisan of ordinary skill to use eslicarbazepine acetate to treat patients intractable to oxcarbazepine without undue experimentation.

3. The #781 Patent (Formulation)

a. Prior Art

109) The #781 patent claims priority to Provisional Application No. 60/982,790 filed on October 26, 2007.[7] JTX 10.

1) The #646 Patent

110) The #646 patent qualifies as prior art to the #781 patent. DTX 427. The #646 patent discloses the compound eslicarbazepine acetate and teaches that it

[7] Although these is some dispute over the priority date, Bial represents that the difference in the priority dates does not matter for the asserted references. D.I. 262 ¶ 192. Thus, I will use October 26, 2007 for the priority date.

can be used to treat epilepsy. DTX 427 3:52–56, 1:11–16. The #646 patent also discloses the use of excipients to make a pharmaceutical composition of eslicarbazepine acetate. DTX 427 5:63–6:5; Tr. at 658:9–13 (McConville).

2) Almeida 2002

111) Almeida 2002 was published in 2002 and qualifies as prior art to the #781 patent. PTX 329. The Patent Office was not made aware of Almeida 2002 during the prosecution of the #781 patent. Tr. at 838:22–39:4 (Williams). Almeida 2002 discusses the results of a safety study of eslicarbazepine acetate. PTX 329 at 5; Tr. at 170:3–8 (Soares da Silva). Almeida 2002 reports a T_{max}[8] for the formulation between .75 and 4 hours. PTX 329 at 5. Approximately a .75 hour T_{max} is consistent with an immediate release profile. Tr. at 672:18–24 (McConville); Tr. at 825:10–12 (Williams). No expert provided an opinion about the dissolution profile of a drug with a T_{max} of four hours. *See* Tr. at 825:131–5 (Williams declining to testify about whether a T_{max} of four hours is consistent with immediate release). Thus, I find that an artisan of ordinary skill reading Almeida 2002 would conclude that the formulation of the compound in the study is consistent with an immediate release formulation.

[8] T_{max} is the time at which C_{max} is achieved. Tr. at 672:17–18 (McConville).

112) Almeida 2002 teaches that administering 1,200 mg of eslicarbazepine acetate, and 1,200 mg is a high drug load. *See* Tr. at 660:14–17 (McConville); *see also* Tr. at 668:25–69:2 (Bial's counsel). Neither party has established whether the study in Almeida 2002 discloses administering 1,200 mg in a single tablet or in multiple tablets. *See* Tr. at 711:9–12:7 (McConville). Thus, Almeida 2002 does not explicitly disclose a high drug load formulation containing eslicarbazepine acetate in a single tablet.

3) Almeida 2003

113) Almeida 2003 was published in 2003 and qualifies as prior art to the #781 patent. PTX 330. The Patent Office was not made aware of Almeida 2003 during the prosecution of the #781 patent. Tr. at 838:22–39:4 (Williams). Almeida 2003 discloses the results of a Phase 1 "single–dose study" where healthy volunteers were administered a "single dose" of eslicarbazepine acetate. Tr. at 761:21–62:1 (Wheless). Almeida 2003 discusses the use of tablets with lower doses and presumedly multiple tablets were administered at once to achieve the required dose. *See* PTX 330 at 3; Tr. at 830:7–15 (Williams). Thus, Almeida 2003 does not disclose a high drug load formulation containing eslicarbazepine acetate in a single tablet.

4) WO #294

114) WO 2005/092294 (WO #294) is titled "Oral Matrix Formulations Comprising Licarbazepine" and qualifies as prior art to the #781 patent. DTX 117. WO #294 discloses a tablet formulation of licarbazepine that is a mixture containing the s-enantiomer of eslicarbazepine. DTX 117 at 2. WO #294 discloses the use of "binders, glidants, and disintegrants" in the tablets of licarbazepine. Tr. at 677:7–14 (McConville); DTX 117 at 10. The tablet disclosed in WO #294 is a bilayer tablet where one of the independent layers is "immediate release." Tr. at 676:14–18 (McConville). WO #294 explains that at least 90% of the drug in the immediate release layer is provided within half an hour, consistent with the standard definition of an immediate-release dosage form. Tr. at 676:9–13 (McConville). Although McConville testified that the overall tablets of WO #294 had "55 to 80 precent" drug load, he did not testify that the immediate-release portion on its own contained any particular drug load. *See* Tr. at 675:25–76:4.

5) Franke

115) Franke et al US 2004/0185095 (Franke) was published on September 23, 2004 and qualifies as prior art to the #781 patent. DTX 122. Franke discloses pharmaceutical compositions with 60 to 95 wt % of oxcarbazepine and 0.05 to 4 wt % of disintegrant. DTX 122 at ¶¶ 33–37. Figure 3 of Franke discloses immediate release formulations where 90% of the drug is released in 15 minutes. Tr. at

682:5–10 (McConville explaining the dissolution profile is consistent with an immediate release formulation); DTX 122 at Fig. 3. Franke also explains that Franke's composition releases 85 to 95% of the active compound within 30 minutes. DTX 122 ¶¶ 21–26. This release profile is consistent with the FDA's definition of immediate release. *See* Tr. at 648:9–17 (McConville). Franke further discloses that the release profile of the composition is "only slightly below that of tablets commonly marketed" and actually disparages "typical sustained release formulations" as "ineffective." DTX 122 ¶ 20. Thus, Franke discloses an immediate release formulation. The dissolution conditions in Franke are different from the dissolution conditions for the #781 patent, but the conditions in Franke are standard test parameters for oxcarbazepine. Tr. at 683:13–21 (McConville).

116) Although Franke does not disclose a formulation containing eslicarbazepine acetate, it discloses a formulation with oxcarbazepine, which is a compound with a solubility similar to the solubility of eslicarbazepine acetate. *See* 682:1–4 (McConville explaining that oxcarbazepine is classified as a poorly soluble drug of the same class as eslicarbazepine acetate). Thus, Franke discloses a formulation with a high load of a low solubility drug with an immediate release dissolution profile. *See* Tr. at 695:20–23 (McConville).

6) Dudhara

117) Dudhara et al US 2003/0175353 (Dudhara) was published on September 18, 2003 and qualifies as prior art to the #781 patent. DTX 123. Dudhara discloses compositions, i.e., tablets, of carbamazepine with 60–85 wt % of carbamazepine and 0.5–5 wt % croscarmellose sodium. DTX 123 at ¶ 26. And Dudhara teaches a controlled release formulation. *See* DTX 123 ¶¶ 9–13. Dudhara explains that its drug delivery system avoids the disadvantages associated with fast drug absorption time and high peak plasma levels. DTX 123 ¶ 3. Thus, Dudhara does not teach immediate release. *See* Tr. at 834:2–14 (Williams).

7) HPE

118) The Handbook of Pharmaceutical Excipients (HPE) was published in 2000 and qualifies as prior art to the #781 patent. DTX 107. HPE is a "go-to" reference for pharmaceutical formulation scientists that describes the excipients that one would need to make any type of dosage form, i.e., immediate or sustained release. Tr. at 677:15–23 (McConville). It also offers weight percentage recommendations for excipients. Tr. at 689:15–24 (McConville). Although no reference discloses the exact amounts of the remaining excipients, an artisan of ordinary skill could use the HPE to pick the amounts of excipients to use. *See* Tr. at 689:15–24, 694:1–5 (McConville).

b. Obviousness

119) Asserted claim 17 read in conjunction with independent claim 1 reads:

> A pharmaceutical composition consisting essentially of eslicarbazepine acetate in combination with a binder and a disintegrant, wherein eslicarbazepine acetate is present in an amount of from 80 to 90 wt%, the binder is present in an amount of from 3 to 10 wt%, and the disintegrant is present in an amount of from 3 to 10 wt%, and wherein the pharmaceutical composition exhibits a dissolution of at least about 60% at about 30 minutes at a temperature of 37±0.5° C. and a pH of about 4.5 using a paddle apparatus at a speed of about 100 rpm, further comprising a lubricant, and/or glidant.

120) The #781 patent is directed to "high drug loaded pharmaceutical compositions containing the active drug substance eslicarbazepine acetate, exhibiting an immediate–release dissolution profile with certain excipients and excipient ranges." Tr. at 290:20–23 (Koleng). "High drug load" refers to the requirement that 80 to 90 wt % of the pharmaceutical composition is eslicarbazepine acetate. Tr. at 290:24–91:3 (Koleng); *see also* Tr. at 652:12–13 (McConville). "Immediate release"[9] refers to "the requirement that the dissolution of the pharmaceutical composition is at least 60 percent at about 30 minutes under the test conditions listed in the claim." Tr. at 291:4–9 (Koleng); *see also* Tr. at 652:15–24 (McConville).

[9] The FDA defines immediate release as 85% of the drug dissolving in 30 minutes. Tr. at 648:9–17 (McConville). McConville clarified that the dissolution profile in the claim is a bit slower than the FDA's definition but is still consistent with an immediate release. Tr. at 652:17–20.

121) Excipients are the "nondrug substance" of a pharmaceutical composition and are usually "inactive or inert." Tr. at 293:18–20 (Koleng).

122) A diluent is an excipient added to a pharmaceutical formulation to "bulk it up." Tr. at 295:1–2 (Koleng); PTX 1214 at 100; JTX 10 at 8:43–45. A binder is a material added to a pharmaceutical formulation to add cohesiveness to hold the components of the composition together. Tr. at 295:19–22 (Koleng); PTX 1214 at 111; JTX 10 at 6:53–54. A lubricant is a material added to a pharmaceutical formulation to reduce friction within a formulation. Tr. at 295:25–96:2 (Koleng); PTX 1214 at 116; JTX 10 at 7:48–53. A glidant is a material added to a pharmaceutical formulation to improve powder flow. Tr. at 296:8–9 (Koleng); PTX 1214 at 121; JTX 10 at 8:21–23. A disintegrant is a material added to a pharmaceutical formulation to help it break up after administration once it hits an aqueous environment (e.g., the liquid in the stomach after the tablet is swallowed). Tr. at 296:13–17 (Koleng); PTX 1214 at 114; JTX 10 at 5:54–55.

123) I construed "a pharmaceutical composition consisting essentially of" as "a pharmaceutical composition that consists at the very least of eslicarbazepine acetate and can consist of other ingredients but only if those other ingredients do not materially affect the basic and novel properties of the claimed composition." D.I. 193.

124) I find that Alkem has shown by clear and convincing evidence that (1) Almeida 2002 disclosed an immediate release formulation with eslicarbazepine acetate as the active ingredient and administering a high drug load even if not all contained in one tablet, *see* Tr. at 672:18–24 (McConville); Tr. at 825:10–12 (Williams), (2) Franke disclosed an immediate release formulation with a high drug load of a compound that has comparable solubility to eslicarbazepine acetate, *see* Tr. at 682:5–10, 695:20–23 (McConville), and (3) the HPE discloses information regarding the remaining excipient amounts, *see* Tr. at 689:15–24, 694:1–5 (McConville).

125) A formulation scientist would consider patient compliance and convenience when formulating a pharmaceutical composition. Tr. at 694:16–95:1 (McConville); Tr. at 842:20–23 (Williams). Administering the required drug load in a single tablet is the "gold standard," Tr. at 694:19–23 (McConville), or "optimum," Tr. at 843:3–6 (Williams). Thus, I conclude that a formulator would have been motivated to make a single tablet containing 1,200 mg of eslicarbazepine acetate after reading Almeida 2002. *See* Tr. at 712:1–7 (McConville testifying that "I do know that the [Almeida 2002] results point to a single oral dose of a particular amount of drug. That would motivate me to make a single tablet containing that amount of drug"). Because the parties agree that 1,200 mg is a high drug load, I find that Alkem has shown by clear and convincing

evidence that an artisan of ordinary skill would have been motivated by Almeida 2002 to create an immediate release formulation with a high drug load of eslicarbazepine acetate in a single tablet. Further, an artisan of ordinary skill would have been motivated to formulate this composition with eslicarbazepine acetate accounting for 90 wt % because, if excipients accounted for more than 10 wt %, the tablet would be too big to swallow. Tr. at 709:11–13 (McConville).

126) Franke discloses pharmaceutical compositions of oxcarbazepine. DTX 122. Oxcarbazepine is used to treat epilepsy and is structurally similar to eslicarbazepine acetate. Tr. at 695:20–23 (McConville). Eslicarbazepine acetate and oxcarbazepine both exhibit low solubility. *See* Tr. at 682:1–4 (McConville). I find that an artisan of ordinary skill would have had a reasonable expectation of success in achieving the claimed invention because oxcarbazepine (Franke reference) was successfully formulated with a comparable drug load and excipients in the claimed ranges to be immediate release. *See* 679:13–80:7 (McConville discussing the Franke reference); Tr. at 694:1–5 (McConville discussing what was known in the art about excipients).

127) Further, in view of the ranges disclosed in the HPE, an artisan of ordinary skill would be able to "select the right excipients to arrive at that profile with that high drug load in a single tablet[.]" Tr. at 654:5–14 (McConville). Even if some experimentation would be required, *see* Tr. at 823:5–10 (Williams), the

required experimentation would not be undue, *see* Tr. at 689:15–90:22 (McConville explaining how an artisan of ordinary skill would adjust the amounts based on the HPE without need undue experimentation); *see also* DTX 122 ¶ 20 (Franke reference disclosing that immediate release oxcarbazepine formulations are common). Accordingly, I find that Alkem has shown by clear and convincing evidence that an artisan of ordinary skill would have had a reasonable expectation of success for creating the formulation described in claim 17 of the #781 patent.

c. Objective Indicia of Nonobviousness

128) Bial points to two objective indicia of nonobviousness: unexpected results and copying.

129) With respect to unexpected results, Lima, a named inventor on the #781 patent, testified that he was surprised when his team finally manufactured the composition because they experienced "significant challenges" related to "the characteristics" of eslicarbazepine acetate, including poor bulk density, poor flowability, and poor water solubility. Tr. 174:17–75:20; *see also* Tr. at 182:2–13 (Lima testifying, "We used multiple formulations, multiple approaches, . . . performed several experiments, . . . used different strategies, and sometimes a combination of the strategies[.]"). But I find that this testimony is not clearly at odds with McConville's testimony. McConville explained that a formulator would start with excipients in the range recommended by the HPE and then adjust the

amounts or switch to a different excipient as necessary. Tr. at 690:10–22. He also testified that high drug loads of several compounds that "fall into the bio classification system . . . that have low solubility" are used for the treatment of epilepsy, so an artisan of ordinary skill would know that use of a disintegrant is necessary. Tr. at 694:6–11. And this testimony is corroborated by Franke. *See* DTX 122. Thus, I do not find Lima's cursory comment about his surprise to be probative of nonobviousness. *See Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) ("Unexpected results are shown in comparison to what was known[.]").

130) With respect to copying, it is undisputed that Alkem designed its formulation to be similar to APTIOM®. Tr. at 400:17–01:3 (Chhabra). But I do not find that fact to be probative of nonobviousness since "a showing of bioequivalence is required for FDA approval" of Alkem's tablet formulation. *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

III. LEGAL STANDARDS

A. Infringement

1. Direct Infringement

Analyzing infringement involves two steps. The first step is to construe disputed patent terms consistently with how they would be understood by an

artisan of ordinary skill. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The second step is to determine whether the accused products or methods infringe the patent by comparing those products or methods to the construed claims. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The first step in the infringement analysis is a question of law; the second is a question of fact. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). A patentee bears the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). Direct infringement requires that "every limitation set forth in a claim . . . be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (citation omitted).

When the ANDA specification does not answer the question of infringement, "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Glaxo*, 110 F.3d at 1570. In such cases, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id.*

2. Induced Infringement

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). A finding of inducement requires establishing an underlying act of direct infringement, that the defendant had knowledge of or was willful blind to the direct infringement, and that the defendant's specific intent was to encourage the acts that constituted direct infringement. *See DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1303, 1306 (Fed. Cir. 2006) (en banc in relevant part). "Where the proposed label instructs users to perform the patented method[,] the proposed label may provide evidence of the ANDA applicant's affirmative intent to induce infringement. When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, the label must encourage, recommend, or promote infringement. The contents of the label itself may permit the inference of specific intent to encourage, recommend, or promote infringement." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018) (internal quotation marks, citations, and original alterations omitted).

B. Inalidity

1. Obviousness

Under § 103 of the Patent Act, a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 17–18 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders recourse to common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was

obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

"While the ultimate determination of obviousness under § 103 is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others." *Daiichi*, 619 F.3d at 1352.

2. Written Description

Section 112 of the Patent Act requires that the specification of a patent "contain a written description of [(1)] the invention, and of [(2)] the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 (2006). Courts refer to these two requirements respectively as adequate written description and enablement.

The "hallmark" of an adequate written description is "disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). A patent must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" to satisfy the written description requirement. *Id.* An applicant establishes it was in possession of the invention "by describing the invention[] with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis omitted). This description can be made using "words, structures, figures, diagrams, formulas, etc." *Id.* A patentee can also "rely on information that is 'well-known in the art' to satisfy written description." *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012) (citation omitted). A challenger to the patent must prove invalidity based on inadequate written description by clear and convincing evidence. *Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005). Whether the written description requirement has been met is a question of fact. *Id.*

3. Enablement

To satisfy § 112's enablement requirement, the written description must provide a description that enables an artisan of ordinary skill to practice the full scope of the claimed invention without undue experimentation. *Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). "That some

experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive." *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations[,]" including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

"Tossing out the mere germ of an idea does not constitute enabling disclosure[;]" instead "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). "[T]hat a specification need not disclose what is well known in the art . . . is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *Id.* "[W]hen there is no disclosure . . . of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." *Id.* A "specification [that]

provides only a starting point, a direction for further research" is not enabled. *See id.*

A challenger must prove invalidity based on non-enablement by clear and convincing evidence. *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). "Enablement is a question of law based on underlying facts." *Wyeth & Cordis*, 720 F.3d at 1384.

IV. CONCLUSIONS OF LAW

A. Infringement

1. The #954 Patent (Method of Treatment)

Bial contends that Alkem will induce infringement of claim 20 of the #954 patent with its ANDA. Alkem disputes only that it infringes claim 20's limitation "wherein the subject has previously been treated with oxcarbazepine." D.I. 293 ¶ 8. Alkem argues, and I have already found as a factual matter, that Bial failed to establish by a preponderance of the evidence that Alkem specifically intends to encourage healthcare providers to prescribe its generic product to treat patients who are intractable to oxcarbazepine. Accordingly, Bial has failed to establish infringement of claim 20. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) (The "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven."); *Vanda*, 887 F.3d at 1129 ("It also must be established that the defendant possessed specific intent to encourage another's

infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement." (internal quotation marks and citation omitted)).

2. The #781 Patent (Formulation)

Bial contends that Alkem's ANDA will infringe claim 17 of the #781 patent. Alkem contests infringement of claim 17 only with respect to the limitation: "consisting essentially of eslicarbazepine acetate in combination with a binder and a disintegrant." D.I. 239 ¶ 10. Alkem frames its argument in these words:

> Alkem does not dispute that all of the claimed ingredients are present in its ANDA product. But Plaintiffs must also show that there are no unclaimed ingredients or, if there are, that any such unclaimed ingredient does not materially affect the basic and novel properties of the claimed composition. They did meet that burden.
>
> First, Plaintiffs failed to show the absence of unclaimed ingredients. While Plaintiffs' expert labeled the 2.18 wt % microcrystalline cellulose ("MCC") in Alkem's ANDA product a "disintegrant," the record shows that MCC does not act as a disintegrant at such a low amount, and that it instead serves as a diluent in Alkem's product, consistent with its identification in Alkem's ANDA.

D.I. 265 at 17–18 (citation omitted).

This argument fails because I found as a factual matter that that Bial established by a preponderance of the evidence that microcrystalline cellulose acts a disintegrant in Alkem's ANDA product.

B. Validity

1. The #287, #354, and #536 Patents (Methods of Dosing)

Alkem contends that the claims in the once-daily patents are invalid as obvious in light of four prior art references: the #646 patent, Almeida 2002, Almeida 2003, and the Trileptal® label.[10] But I have found as a factual matter that these references, considered individually or collectively, do not disclose that once-daily dosing of eslicarbazepine acetate is efficacious to treat partial-onset seizures, and that Alkem therefore did not show by clear and convincing evidence that an artisan of ordinary skill would have had a reasonable expectation of success in using once-daily dosing of eslicarbazepine acetate to treat partial-onset seizures. And I also found that the so-called secondary considerations of unexpected results, industry skepticism, and commercial success support the conclusion that an artisan of ordinary skill would not have viewed the methods of dosing patents as obvious. For these reasons, I conclude as a matter of law that Alkem failed to establish that representative claim 3 of the #287 patent and thus the other asserted claims from the once-daily patents are invalid as obvious under § 103.

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[10] In a footnote, Alkem suggests that these claims are not patent eligible. D.I. 263 at 7 n.2. I decline to entertain this cursory argument made in passing. *See John Wyeth & Bro. Ltd. v. CIGNA Int'l Corp.*, 119 F.3d 1070, 1076 n.6 (3d Cir. 1997) ("[A]rguments raised in passing (such as, in a footnote), but not squarely argued, are considered waived."); *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006) ("[A]rguments raised in footnotes are not preserved.").

2. The #954 Patent (Method of Treatment)

a. Written Description

Alkem contends that claim 20 of the #954 patent is invalid because it has inadequate written description. Specifically, it argues that the patent's specification

> does not provide any example relevant to treating an intractable epilepsy condition, and most notably does not provide any example in which a patient (or animal model) intractable to oxcarbazepine is treated with eslicarbazepine acetate. Further, because oxcarbazepine and eslicarbazepine acetate metabolize into the same active metabolite, MHD, a POSA would not expect eslicarbazepine acetate to be effective in a patient who is intractable to oxcarbazepine.

D.I. 263 at 26–27 (citation omitted).

Bial counters that

> The [#]954 patent's example reporting the brain access of eslicarbazepine and R-licarbazepine further informs a skilled artisan that oxcarbazepine and eslicarbazepine acetate would not yield the same treatment results because eslicarbazepine is not a substrate for P-gp, while R-licarbazepine and oxcarbazepine are. This disclosure would have led a skilled artisan to conclude that eslicarbazepine acetate could effectively treat an intractable epilepsy condition (consistent with Phase II clinical study data demonstrating efficacy in intractable epilepsy patients) even where oxcarbazepine did not.

D.I. 256 at 32 (citation omitted).

"An inventor need not prove that a claimed pharmaceutical compound actually achieves a certain result. But when the inventor expressly claims that result, [Federal Circuit] case law provides that such result must be supported by adequate disclosure in the specification." *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021) (internal quotation marks, citation, and alteration omitted). Since Bial claims treatment of partial-onset seizures with eslicarbazepine acetate in patients intractable to oxcarbazepine, "[w]hat matters for purposes of the [written description] inquiry in this case is whether, at the time of filing the disclosure . . . a skilled artisan could deduce simply from reading the specification that [eslicarbazepine acetate] would be a therapeutically effective treatment for [partial-onset seizures in patients intractable to oxcarbazepine]." *Id.* at 1343–44.

I have found as a factual matter that Alkem has established by clear and convincing evidence that no data in the patent suggests that eslicarbazepine acetate could be used to effectively treat a patient intractable to oxcarbazepine. Instead, the patent offers at most a research hypothesis. Thus, "[r]egardless of whether [Bial] had in fact hypothesized or even conceived of the idea of treating [partial-onset seizures in patient intractable to oxcarbazepine] with [eslicarbazepine acetate] . . . the law is clear that a patent cannot be awarded for mere theoretical research without more[.]" *Id.* at 1344.

Accordingly, I find that Alkem has established by clear and convincing evidence that an artisan of ordinary skill would not conclude that the inventor was in possession of the invention, and thus, claim 20 of the #954 patent is invalid for lack of adequate written description under § 112. *See Ariad*, 598 F.3d at ("Patents are not awarded for academic theories . . . [and] research hypotheses do not qualify for patent protection[.]").

b. Enablement

Alkem also contends that the #954 patent is "invalid for lack of enablement." D.I. 263 at 32. Specifically, it contends that the patent does not explain how to treat a patient with eslicarbazepine acetate who is intractable to oxcarbazepine and that therefore an artisan of ordinary skill could not practice the method of claim 20 without undue experimentation. D.I. 263 at 32. Bial argues in response that an artisan of ordinary skill would have known how to treat patients using eslicarbazepine acetate generally and that the steps for treating a patient intractable to oxcarbazepine are the same as the steps for treating other patients, so an artisan could have treated patients intractable to oxcarbazepine without undue experimentation. D.I. 256 at 31.

Alkem's enablement argument is based on the same theory as its written description argument: the patent does not teach how to treat a patient who is intractable to oxcarbazepine and is "at best" a "hypothesis for further

investigation." D.I. 263 at 32–33. "[W]here there is no indication that one skilled in the art would accept without question statements as to the effects of the claimed drug products and no evidence has been presented to demonstrate that the claimed products do have those effects, an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (internal quotation marks, citation, and alterations omitted). I have found as a factual matter that Alkem has shown by clear and convincing evidence that the patent does not present evidence to demonstrate that eslicarbazepine acetate would have the claimed effect of treating partial-onset seizures in patients intractable to oxcarbazepine and is solely a research hypothesis.

Bial argues that, because an artisan of ordinary skill would understand how to dose eslicarbazepine acetate for intractable patients, undue experimentation would not be required to practice the claim. D.I. 256 at 31. Although a "patent does not need to guarantee that the invention works for a claim to be enabled," *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014), a patent must have sufficient disclosures such that a "skilled artisan would not have questioned the utility of the claimed formulation and would be able to make and use the claimed invention without undue experimentation," *see Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (finding the patent enabled

when it disclosed "actual *in vitro* and *in vivo* data, showing that increasing the amount of BAK unexpectedly increased the permeability of bimatoprost across ocular membranes"). Here, because I have found as a factual matter that the data disclosed in the written description fails to convey that eslicarbazepine acetate would treat patients intractable to oxcarbazepine, I conclude that an artisan of ordinary skill would require undue experimentation to practice the claim.

I find that Alkem has shown by clear and convincing evidence that the method claimed by #954 patent is at best plausible, thus failing to satisfy the enablement requirement under § 112. *See Rasmusson*, 413 F.3d at 1325 ("If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. . . . That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."). Accordingly, I conclude as a matter of law that Alkem has established by clear and convincing evidence that claim 20 of the #954 patent is invalid under § 112 for lack of enablement.

3. The #781 Patent (Formulation)

Alkem contends that the #781 patent is invalid in light of seven prior art references: the #646 patent, Almeida 2002, Almeida 2003, WO #294, Franke, Dudhara, and HPE.

Bial argues that the references do not disclose a high drug load formulation of eslicarbazepine acetate with an immediate-release dissolution profile. D.I. 256 at 35. I found as a factual matter, however, that Alkem established by clear and convincing evidence that Almeida 2002 disclosed administering a large dose of eslicarbazepine acetate with an immediate-release dissolution profile.

Bial further argues that Alkem failed to establish that a skilled artisan would have been motivated to combine the prior-art disclosures with a reasonable expectation of success. D.I. 256 at 35. But I found as a factual matter that Alkem established by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine the teachings of the prior art after reading Almeida 2002, would have had a reasonable expectation of success of achieving the claimed composition given the Franke reference, and could have achieved the claimed formation without undue experimentation given HPE. I note also that Almeida 2002 was not considered by the patent examiner during prosecution. *See Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 111 (2011) (explaining that "invalidity defense by clear and convincing evidence may be easier to sustain" when the "PTO did not have all material facts before it" during prosecution).

Bial argues that the secondary considerations of unexpected results and copying counsel against a finding of obviousness. D.I. 256 at 51–52. But I have found as a factual matter that neither consideration is probative of nonobviousness.

In short, I have found as a factual matter that Alkem established by clear and convincing evidence that a formulator would have been motivated to make a single tablet containing 1,200 mg of eslicarbazepine acetate after reading Almeida 2002 and that based on the disclosures in Franke and HPE an artisan of ordinary skill would have had a reasonable expectation of success for creating the formulation described in claim 17 of the #781 patent. Accordingly, Alkem established by clear and convincing evidence that claim 17 of the #781 patent is invalid as obvious under § 103.

V. CONCLUSION

For the reasons discussed above, I find that Bial has established that Alkem's ANDA will infringe claim 17 of the #781 patent, but it has not established that Alkem will induce infringement of claim 20 of the #954 patent. I also find Alkem has established that claim 20 of the #954 patent is invalid under § 112 and that claim 17 of the #781 patent is invalid under § 103. But I find that Alkem has not established that claim 3 of the #287 patent, claim 5 of the #354 patent, or claims 7 and 8 of the #536 patent are invalid under § 103.

The Court will issue an Order directing the parties to submit a proposed order by which the Court may enter final judgments consistent with this Opinion.